Disguised Thyroid Disorders

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■ *In six cases of hyperthyroidism and two of chronic thyroiditis herein described, the initial features of the diseases were misinterpreted as attributable to other kinds of illness such as myocardial infarction, gastrointestinal malignant disease, malabsorption syndrome, psychosis, simple exophthalmos and endemic goiter. The characteristic signs and symptoms of hyperthyroidism (in six patients) and chronic thyroiditis (in two patients) were present at the outset but were not identified. Intensive questioning and alertness were required to elicit these characteristics. The symptoms improved or disappeared after the true disease was controlled.*

In the studies of these cases, the usefulness of a number of laboratory tests was illustrated—thyroid suppression studies, 4 to 6-hour and 24-hour radioactive iodine uptake, T_3 uptake by the red cells and determinations of 24-hour urine creatine, antithyroglobulin antibody titer and long-acting thyroid stimulating hormone.

The manifestations of thyroid diseases are many and varied. The term "masked hyperthyroidism" may in part be a reflection of the "masked physician" unless he uses his clinical detective abilities.

THYROID DISEASES may manifest themselves by protean signs and symptoms. Unless the physician is alert for the less common manifestations of thyroid dysfunction, the clinical features may be easily misinterpreted.

In the following illustrative cases, observed in the Thyroid Clinic at Los Angeles County General Hospital, there was a considerable variety of initial signs and symptoms referable to thyroid disease. The elucidation of these problems was aided greatly by the use and proper interpretation of appropriate tests of thyroid function, such as 6-hour radioactive iodine uptake, red blood cell uptake (T_3), thyroglobulin antibody titer, thyroid suppression studies, long-acting thyroid stimulating factor (LATS) and determination of 24-hour urine creatine.

CASE 1. A 54-year-old Caucasian woman was admitted October 15, 1963, with complaint of progressive loss of weight, weakness and intermittent episodes of diarrhea for approximately one year. On admission her weight was 65 pounds. She had obvious cachexia and pronounced wasting. The thyroid gland was palpable but not thought to be enlarged. The initial impression was of possible gastrointestinal tract malignant disease but x-ray studies, including the chest, the upper gastrointestinal tract and barium enema films, showed no abnormality. The patient continued to lose weight. Two weeks after admission, thyroid disease was suspected and the suspicion was confirmed by a 24-hour I^{131} uptake of 82 per

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Presented before the Section on Internal Medicine on a program prepared in cooperation with the California Society of Internal Medicine at the 93rd Annual Session of the California Medical Association, Los Angeles, March 22 to 25, 1964.

TABLE 1.—*(Case 1) Laboratory and Clinical Data 54-year-old White Woman*

Initial diagnosis: Cancer of the gastrointestinal tract
Final diagnosis: Hyperthyroidism

	1963				1964
	10/15	10/29	11/26	12/18	1/6
PBI (mcg per 100 ml)		9.3	5.6		4.5
Cholesterol (mg per 100 ml)		95			221
I^{131} uptake (per cent 24 hr.)		82			
Body weight (pounds)	65	61	82	96	102½
Therapy		Methimazole Diphenhydramine Reserpine Desiccated thyroid			

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine

cent and by positive results of other tests (Table 1). Administration of methimazole (Tapazole®) was begun and the patient gained weight rapidly and became euthyroid. She received I^{131} therapy in December, 1964.

Comment. Because classic symptoms of hyperthyroidism, such as increased sweating, hyperactivity or enlargement of the thyroid gland, were not present at the time this patient was first observed, the correct cause of the loss of weight was not seriously considered until 14 days had elapsed. Early recognition of problems of this type is important, for the situation is almost an emergency. The patients are acutely ill, are in severe negative nitrogen balance, and therapy should be begun at once.

CASE 2. A 29-year-old Negro man was admitted on June 14, 1963, with chief complaint of progressive bulging of the eyes of three months' duration. Interview elicited no mention of any recent symptoms referable to possible hyperthyroidism. No overt manifestation of hyperthyroidism was noted clinically, although some of the physicians who observed the patient considered him overly active in behavior.

On physical examination bilateral exophthalmos with moderate chemosis and infiltration was noted. The right eye was more prominent than the left. The thyroid gland was palpable but not enlarged. Results of thyroid function tests were within normal limits: Protein-bound iodine (PBI) was 7.9 mcg per 100 ml, cholesterol content was 193 mg per 100 ml and 24-hour radioactive iodine (RAI) uptake was 22 per cent. However, to fully evaluate thyroid function, a suppression study using liothyronine (Cytomel®), 75 mcg daily for one week, was carried out. The I^{131} uptake then was 21 per cent in 24 hours. A T_3 uptake test was also obtained and the value was 24.8 per cent (normal 10.3 to 14.3 per cent). With this proof of hyperthyroidism, thyroid suppression thereby was begun with Tapazole.® When the patient became euthyroid, as determined by serial measurements of T_3 uptake, he was given a therapeutic dose of 15 millicuries of I^{131}. Eye measurements improved concomitantly with antithyroid therapy (Table 2).

Comment. The correct diagnosis of hyperthyroidism in this case required the use of the I^{131} suppression test.[2] The failure to suppress proved that the gland was functioning autonomously and independently of pituitary control.[8] The significance of the exophthalmos was then clear, and proper antithyroid therapy gave good results. The elevated T_3 uptake provided further substantiation for the diagnosis of hyperthyroidism and proved a valuable indicator of adequacy of antithyroid treatment before definite therapy with radioactive iodine. An interesting feature in this case was the change of the initially negative long-acting thyroid stimulating bioassay to positive during the course of therapy with antithyroid drugs.

CASE 3. A 67-year-old Caucasian man was admitted on September 4, 1963, with complaint of sudden onset of pain in the left side of the chest and of diaphoresis beginning 12 hours before admission. An electrocardiogram showed S-T elevations in leads II, III and AvF compatible with acute diaphragmatic myocardial infarction, myocarditis or pericarditis. Treatment for acute myocardial infarction was begun. The following day the

TABLE 2.—*(Case 2) Laboratory and Clinical Data 29-year-old Negro Man*

Initial diagnosis: Exophthalmos
Final Diagnosis: Graves' Disease

	1963						
	6/13	6/25	7/31	8/14	9/11	10/30	11/7
PBI (mcg per 100 ml)	7.9		7.3		5.3	3.8	
Cholesterol (mg per 100 ml)	193		193		198	248	
I^{131} uptake (per cent 24 hr.)	22						55
Liothyronine Suppression (per cent 4 hr.)			10				
(per cent 24 hr.)			21				
T_3 uptake (per cent)	24.8			19.4	15.2		15.4
LATS			Negative			Positive	
Exophthalmos Measure—Right eye		22	20	19			
Left eye		22	20	19			
Therapy		Diphenhydramine Methimazole Desiccated thyroid					15 Mc I^{131}

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
T_3=triiodothyronine
LATS=Long acting thyroid stimulating factor

sinus rhythm changed to an uncontrolled auricular fibrillation. This persisted despite digitalization to the point of toxicity. The possibility of thyrotoxic heart disease was then suspected and was further supported by a more detailed history in which loss of weight for a period of six months, muscle weakness, nervousness and intolerance to heat were mentioned. A four-hour I^{131} uptake of 58 per cent confirmed the diagnosis. Thereupon antithyroid therapy and sedation were begun, and within 48 hours the cardiac arrhythmia had been converted to a regular sinus rhythm. Electrocardiograms thereafter showed no further evidence of cardiac disease. Serial serum enzyme studies, glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase (SLDH) were entirely within normal limits. Before treatment the PBI was 13.6 mcg per 100 ml. While receiving therapy the patient rapidly gained 30 pounds and was able to have radioactive iodine treatment on October 22, 1963. At last report he was well maintained on 0.2 gm of desiccated thyroid daily (Table 3).

TABLE 3.—*(Case 3) Laboratory and Clinical Data 67-year-old White Man*

Initial diagnosis: Acute myocardial infarction
Final diagnosis: Thyrotoxic heart disease

	1963							1964
	9/6	9/12	9/18	10/3	10/10	10/22	12/11	1/5
PBI (mcg per 100 ml)	13.6			8.5	5.3		7.2	6.0
Cholesterol (mg per 100 ml)	142						241	245
I^{131} uptake (per cent 4 hr.)		58						
(per cent 24 hr.)		84				71		
Urine creatine (mg/24 hr.)		594						
Therapy		Methimazole Diphenhydramine Reserpine Desiccated thyroid				4.2 Mc I^{131}		
Body weight (pounds)			145	150	158	167	171	175

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
Mc=millicuries

Comment. In this case, the suspected cardiac problem was quickly confirmed by the 4-hour I^{131} uptake,[5] thereby preventing a possible delay in treatment while awaiting determination of the 24-hour uptake of protein-bound iodine (PBI). It is also interesting to note the decided elevation of urine creatine (Table 3), which was indicative of pronounced muscle wasting. The urine creatine determination is occasionally helpful in diagnosis of suspected hyperthyroidism, since it is elevated when muscle wasting is associated with the disease.[7] Also it can be used as a gauge of the efficiency of antithyroid treatment.

CASE 4. A 54-year-old Caucasian woman was originally seen as an outpatient in 1958 for an enlarged thyroid gland. No symptoms or findings of hyperthyroidism were observed. The PBI value was 4.5 mcg per 100 ml at that time. The diagnosis was multinodular goiter and no therapy was given. In 1962 the patient was seen again because of complaint of nervousness and generalized weakness of six months' duration. No considerable increase in the size of the gland was noted. PBI was 4.5 mcg per 100 ml, cholesterol was 310 mg per 100 ml and radioactive iodine uptake was 49 per cent in 24 hours. Further laboratory tests included a reversed albumin-globulin ratio of 3.8:5.0 gm per 100 ml with an elevated gamma globulin fraction which, since the patient was known to be a heavy drinker, was thought to reflect alcoholic cirrhosis. A diagnosis of nontoxic nodular goiter was made and no therapy was recommended.

In September of 1963 the patient complained vaguely of general lethargy and weakness. As she appeared clinically to be hypothyroid, thyroid function tests were carried out, including antithyroglobulin titer determination. The titer was reported at 1:500,000, demonstrating that the problem was chronic thyroiditis or Hashimoto's disease. Desiccated thyroid was given, 0.2 gm daily, and the patient underwent dramatic improvement in wellbeing and vigor. Her physical appearance changed as the thyroid gland shrank in size and her weight dropped from 136 to 114 pounds. The antithyroglobulin antibody titer dropped to 1:200,000 and the PBI rose to 7.3 mcg per 100 ml (Table 4).

Comment. This patient had had hypothyroid disease at least a year before the diagnosis (as evidenced by elevated gamma globulin fraction[3]) and perhaps as far back as 1958. Unless the possibility of Hashimoto's disease is kept in mind (especially in a middle-aged woman with thyroid gland enlargement) it may be overlooked. In our own experience, the variability and the vagueness of presenting symptoms is commonplace. The protein-bound iodine and the radioactive iodine uptake can be high, low or normal, depending on

TABLE 4.—*(Case 4) Laboratory and Clinical Data 54-year-old White Woman*

Initial diagnosis: Simple goiter
Final diagnosis: Hashimoto's thyroiditis

	1958	1962			1964
	5/16	1/3	9/3	9/18	1/21
PBI (mcg per 100 ml)	4.5	4.5	5.0		7.3
Cholesterol (mg per 100 ml)		310	275		318
I^{131} uptake (per cent 24 hr.)		49		19	
Albumin/Globulin ratio		3.8/5.0			
T_3 uptake (per cent)			13.5		
Thyroglobulin Antibody Titer			1:500,000		1:200,000
Therapy			Desiccated thyroid		
Body weight (pounds)			136		114
Serum protein electrophoresis			↑γ globulin		

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
T_3=triiodothyronine
↑γ globulin=increased gamma globulin

TABLE 5.—*(Case 5) Laboratory and Clinical Data 57-year-old White Man*

Initial diagnosis: Involutional psychosis-paranoia
Final diagnosis: Hyperthyroidism

	1963				
	8/21	*8/26*	*9/4*	*11/10*	*12/2*
PBI (mcg per 100 ml)	13.7	12.0	10.0	5.2	
T_3 uptake (per cent)	20.9	17.2	14.5	14.0	
I^{131} uptake (per cent 24 hr.)	54				58
Body weight (pounds)	145	154	159		
Therapy	Methimazole Diphenhydramine Desiccated thyroid				

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
T_3=triiodothyronine

the stage of the disease. Diagnosis depends on demonstration of an elevated antithyroglobulin antibody titer and/or biopsy.[6]

In the foregoing case the morbidity of the disease increased because of delay in diagnosis that might have been made earlier had there been complete diagnostic workup and awareness of the possibility of this condition in this patient.

CASE 5. A 57-year-old Caucasian farmer was brought by his family to the Psychiatric Unit of Los Angeles County General Hospital on August 6, 1963. For the past year he had become increasingly unmanageable due to restlessness, agitation and hyperactivity. He occasionally became combative and his behavior was paranoid. He had twice been at Camarillo State Hospital for alcoholism. After psychiatric evaluation, he was admitted to the ward with a diagnosis of involutional psychosis with paranoid tendencies. On the ward his hyperactivity was quite evident, as he helped the personnel mop floors, wash windows and bus trays. He rarely slept and was constantly asking for extra portions of food. After two weeks of this behavior, a member of the ward staff suspected thyroid disease. Tests done then showed PBI of 13.7 mcg per 100 ml and radioactive iodine uptake of 54 per cent.

The patient was then transferred to the medical division and administration of methimazole (Tapazole®) was begun. He rapidly gained weight and the hypermetabolic state diminished to the point that he could be discharged for observation as an outpatient (Table 5).

Comment. This patient was one of two in the past two years who were seen first on the Psychiatric Ward but later were found to be decidedly hyperthyroid. The mental symptoms of these patients improved greatly with antithyroid treatment, indicating that the primary disturbance was probably owing to thyroid disease. Although the bizarre and erratic behavior of hyperthyroid patients is well known, occasionally this disturbance may still be misinterpreted as a functional rather than an organic illness.

CASE 6. The patient, a 39-year-old Caucasian woman, was admitted on August 12, 1963, with chief complaint of lachrymosis and swelling of the eyelids. She had lost some 100 pounds in nine months on a weight reduction regimen entailing 0.25 gm of desiccated thyroid daily, organic iodides, amphetamine and laxatives. On physical examination, a fine tremor of the hands was noted and her behavior was of neurotic type (which was in keeping with her behavioral history). Bilateral exophthalmosis was present, with severe chemosis and infiltration. Also noted were nodular pretibial infiltrations. Protein-bound iodine was 10.2 mcg per 100 ml, cholesterol 162 mg per 100 ml and butanol extractable iodine (BEI) 8.0 mcg per 100 ml. A four-hour I^{131} uptake was 15 per cent and the 24-hour uptake 28 per cent (Table 6).

The clinical question at this point was whether this patient's obvious exophthalmic problem was secondary to actual hyperthyroidism. The results of blood chemical content determinations could be ascribed to the long term ingestion of desiccated thyroid and organic iodides, and the clinical status of the patient could be due to psychoneurosis or the diet regimen she was following.

A thyroid suppression test with triiodothyronine

TABLE 6.—*(Case 6) Laboratory and Clinical Data 39-year-old White Woman*

Initial diagnosis: Thyrotoxicosis Factitia vs. Graves' Disease
Final diagnosis: Graves' Disease

	1963							1964	
	8/12	8/21	9/4	10/2	10/9	10/31	11/5	1/8	1/16
PBI (mcg per 100 ml)	10.7			4.3	3.4		6.9		
Cholesterol (mg per 100 ml)	162			163			226		
I^{131} uptake (per cent 4 hr.)		15							
(per cent 24 hr.)		28							4
Liothyronine Suppression (per cent 4 hr.)			13						
(per cent 24 hr.)			18						
Exophthalmos Measure—Right eye			29			29			
Left eye			27			30			
Weight (pounds)	135		150				166	171	
LATS	Positive								
Therapy		Methimazole, Diphenhydramine, Desiccated thyroid, Diuretics, Topical steroids				10 Mc I^{131}	Tarsorrhaphy		30 Mc I^{131}

KEY TO ABBREVIATIONS:
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LATS=Long acting thyroid stimulating factor

was carried out. The resultant four-hour I^{131} value of 13 per cent and 24-hour value of 18 per cent indicated autonomous thyroid gland function. A bioassay of the long-acting thyroid-stimulating factor (LATS) was obtained and found to be strongly positive. Administration of methimazole (Tapazole®) was begun. Supportive measures for the eye problem included administration of diuretic agents and topical use of an ophthalmic ointment. Exophthalmos continued undiminished and visual acuity began to decrease. For a time it was feared that corneal ulcerations would develop. Undermining her morale, these complications made the management of the thyroid disease even more difficult. Specialized therapy (reported elsewhere[1]) at last brought the eye problems and the nodular pretibial myxedema under control.

Comment. The correct diagnosis was not only helped by the thyroid suppression studies (which were discussed previously) but also by the assay of the long-acting thyroid-stimulating factor. This latter, a relatively new test, is still confined mainly to research, since it is technically difficult and prohibitively costly. McKenzie[4] and investigators have done much work on LATS and there is reasonably good evidence that it may be the long sought exophthalmic factor.

CASE 7. A 23-year-old Negro woman entered the hospital July 8, 1963, with chief complaint of rapid swelling of the neck that had begun a month before. This had been associated with several days of tenderness to palpation, the pain radiating to the angle of the jaw and ear. On physical examination diffuse enlargement of the thyroid gland was noted. The weight of the gland was estimated at approximately 100 gm. It was not tender to palpation.

Protein-bound iodine was 6.0 mcg per 100 ml, butanol-extractable iodine (BEI) 2.7 mcg per 100 ml, uptake of I^{131} was 13 per cent and of T_3 10.1 per cent. The thyroglobulin antibody titer was 1:32,800. A diagnosis of resolving subacute thyroiditis was made and the patient was discharged. As she desired surgical removal for cosmetic reasons, total thyroidectomy was done, with a preoperative diagnosis of possible thyroid carcinoma. The gross appearance of the gland at operation made the surgeon strongly suspect papillary carcinoma and plans were made to treat the patient with radioactive iodine postoperatively. However, the pathologist reported the microscopic features were those of classic Hashimoto's thyroiditis.

It was at this point that we first saw the patient, and in retrospect the clinical features and the re-

TABLE 7.—*(Case 7) Laboratory and Clinical Data 23-year-old Negro Woman*

Initial diagnosis: Subacute Thyroiditis
Final diagnosis: Hashimoto's Thyroiditis

	1963 7/8	7/15	
PBI (mcg per 100 ml)	6.0		Serum protein electrophoresis—increased gamma fraction
BEI (mcg per 100 ml)	2.7	2.3	Albumin: Globulin—3.7: 5.6 grams/100 ml
Cholesterol (mg per 100 ml)	173		Thymol turbidity—11 units
I^{131} uptake (per cent 24 hr.)	13	10.8	Serologic tests—VDRL positive —Kolmer positive
T_3 uptake (per cent)	10.1		TPI (Treponema Pallidum Immobilization)—negative
Thyroglobulin antibody titer	1:32,800		

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
BEI=butanol extractable iodine
I^{131}=radioactive iodine
T_3=triiodothyronine

sults of laboratory tests were entirely consistent with only one diagnosis—Hashimoto's thyroiditis. The symptoms of gland tenderness with radiation to the ear and the angle of the jaw are not typical of this disease (Table 7).

When last observed the patient was receiving thyroid replacement therapy and doing quite well.

Comment. The wide difference between the PBI and the BEI were a tip-off as to the right diagnosis.[3] In some cases of Hashimoto's disease the BEI (which measures the thyroxine alone) is lower than the PBI, since an enzymatic defect may be present, producing more monoiodotyrosine and diiodotyrosine than thyroxine and causing a higher PBI.

The increased serum globulin with elevated gamma fraction, the elevated thymol turbidity and the false positive response to a serologic test (the treponema immobilization test was negative) are all a reflection of the autoimmune process occurring in Hashimoto's disease.

TABLE 8.—*(Case 8) Laboratory and Clinical Data 58-year-old White Woman*

Initial diagnosis: Gastrointestinal malignancy
Final diagnosis: Thyrotoxicosis

	1964 1/30	2/1	2/18
PBI (mcg per 100 ml)		8.7	
Cholesterol (mg per 100 ml)		110	
I^{131} uptake (per cent 24 hr.)			69
Serum albumin (gm per 100 ml)		1.5	
Body weight (pounds)	88	78	67

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine

CASE 8. A 58-year-old Caucasian woman was admitted on January 30, 1964, because of peripheral edema of two weeks' duration. For about a year she had noted loss of weight and had had recurrent diarrhea. The initial diagnostic impression was that of either a gastrointestinal malignant lesion or a protein-losing enteropathic condition. On admission the patient weighed 88 pounds. Her weight decreased to 67 pounds while she was in the hospital, but the reduction was thought to be due to loss of edematous fluid. At first, investigation was focused on the gastrointestinal tract, with x-ray studies and tests of absorption adequacy. Although a PBI determination was carried out, the result, 8.7 mcg per 100 ml, was not given its proper significance until two and a half weeks later when a radioactive iodine uptake test was done and the amount absorbed was 69 per cent. The total serum albumin was 1.5 gm per 100 ml (Table 8). Because of these factors and voracious eating by the patient, the ward staff began to suspect that the loss of weight might have been due to something besides diuresis. With antithyroid therapy (Tapazole®) her weight increased but she remained in hospital because of severe malnutrition.

Comment. This was another case of hyperthyroidism in which the presenting symptom was severe loss of weight. If the decidedly low serum albumin level had been taken into consideration when the PBI result was evaluated (since it was

the cause of the lower PBI value), perhaps the diagnosis would have been made earlier. We would like to stress again the need for rapid diagnosis and treatment of patients who present with such severe negative nitrogen balance. Such patients are critically ill and need prompt stemming of the disease process.

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